REMARKS/ARGUMENTS

1. Claims 1-3 and 6-8 remain pending. In the Office Action mailed June 18, 2003, claims 1-3 and 6-8 stand rejected, under 35 U.S.C. § 112, first paragraph, for inadequate written description and for lack of enablement, claims 6-8 stand rejected, under 35 U.S.C. § 112, second paragraph, for indefiniteness, and claims 1, 2, and 6-8 stand rejected, under 35 U.S.C. § 103, for obviousness over Capecchi (Scientific American 270: 34-41, 1994) in view of Hussman (Mol. Cell. Endocrinol. 162: 35-43, 2000).

2. In keeping with the restriction election, claims 1, 3, and 6 are currently amended to pertain to the RAMP1 gene, to delete reference to the RAMP3 gene, and, in the case of claim 6, to delete reference to the RAMP2 gene. Independent claims 1 and 3 are also amended as follows: to pertain to genetically modified mice and murine cells, respectively, rather than mammals and animal cells, respectively; to pertain to genetic modifications which are homozygous for disruption of the RAMP1 gene; and to expressly recite the phenotype of exhibiting nondetectable RAMP1 polypeptide activity. Independent claim 3 also now recites a progeny cell. Support for the amendments is found in the specification: for mice, in original claim 2, for murine cells, in original claim 8; for a homozygous disruption of the gene causing nondetectable RAMP1 polypeptide activity, at page 6, lines 5-7, for RAMP1 polypeptide activity, at page 7, lines 24-29, and for progeny cells, at page 6, line 29, to page 7, line 13. Dependent claim 7 is currently amended to provide proper antecedent basis in keeping with amendment to claim 6 from which claim 7 depends.

3. Written Description. Claims 1-3 and 6-8 stand rejected for inadequate written description on the basis that the claim fails to recite a phenotypic limitation that would reasonably convey to one skilled in the art that Applicants had possession of all subject matter encompassed by the claims. Claims 6-8 also stand rejected on the bass that the claims encompass any RAMP1 gene. Applicants have added the phenotypic limitation to the relevant independent claims 1 and 3 that the claimed mice and claimed murine cells, or their progeny, exhibit non-detectable RAMP1 polypeptide activity, which can be measured as described in the specification at page 7, lines 23-30. Applicants also note that claim 1 and 6 now recite "the RAMP1 gene" rather than "a RAMP1 gene" when referring to the disruption of the murine RAMP1 gene. For all of the above reasons, Applicants request that the rejections for inadequate written description be withdrawn.

4. Enablement. Claims 1-3 and 6-8 stand rejected for lack of enablement on the basis that the specification fails to enable anything but genetically-modified mice and murine cells homozygous for the murine RAMP1 gene disruption wherein the mouse exhibits altered liver and muscle function. Applicants note that, in view of the current amendments, all claims are limited to genetically-modified mice or murine cells homozygous for the murine RAMP1 gene disruption. With respect to the phenotypic limitation of these mice, applicants have added recitation of a phenotype that the claimed mice and cells no longer exhibit RAMP1 polypeptide activity as a result of the homozygous gene disruption. In view of these amendments, Applicants request reconsideration and withdrawal of this rejection.

5. Indefiniteness. Applicants have added the limitation "cultured" to claim 6 in keeping with the Examiner's suggestion. Withdrawal of this rejection is respectfully requested.

6. Obviousness. Claims 1, 2, and 6-8 stand rejected on the basis that the general methodology teachings of homologous recombination disclosed in Capecchi, in view of the RAMP1 sequence disclosed in Hussman, render the claims obvious. In view of the current amendments, limiting the claimed subject matter to mice and murine cells homozygous for the RAMP1 gene disruption, Applicants traverse this rejection. Nowhere in Capecchi or Hussman is it disclosed that genetically-modified mice and murine cells homozygous for disruption of the murine RAMP1 gene (a "RAMP1 knockout") would be viable if produced. One skilled in the art would not be able to predict, prior to their actual generation, whether a RAMP1 knockout mouse and murine cell would be viable and could be made. In support of this position, Applicants enclose Zambrowicz and Sands (Nature Reviews – Drug Discovery 2: 38-51, 2003) which reviews knockout information for genes targeted by best selling drugs. As provided in Table 8, there are listed approximately 32 targets for which knockout information is available. Of these, 7 knockouts produced embryonic or early lethality. In addition, knockout information was not available for 8 targets. It is likely that the reason for no reports on at least some of these 8 targets of high interest is because attempts to create knockouts failed due to lethality. This review demonstrates that the possibility of failing to be able to obtain a knockout of interest for lethality reasons is very significant. Accordingly, having information on knockout technology and the RAMP1 gene, as arguably provided in combination by Capecchi and Hussman, in no way discloses or suggests that the claimed genetically-modified mice and murine cells could be successfully made and would be viable. Accordingly, Applicants request reconsideration and withdrawal of the rejection for obviousness.

6. Applicants believe that the amendments hereinabove to the claims place the Application in condition for immediate allowance. Therefore, entry of the amendments hereinabove and reconsideration of the Office Action mailed June 18, 2003 are respectfully requested. Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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